

Abnormal mandibular growth and the condylar cartilage

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SUMMARY Deviations in the growth of the mandibular condyle can affect both the functional occlusion and the aesthetic appearance of the face. The reasons for these growth deviations are numerous and often entail complex sequences of malfunction at the cellular level.

The aim of this review is to summarize recent progress in the understanding of pathological alterations occurring during childhood and adolescence that affect the temporomandibular joint (TMJ) and, hence, result in disorders of mandibular growth. Pathological conditions taken into account are subdivided into (1) congenital malformations with associated growth disorders, (2) primary growth disorders, and (3) acquired diseases or trauma with associated growth disorders.

Among the congenital malformations, hemifacial microsomia (HFM) appears to be the principal syndrome entailing severe growth disturbances, whereas growth abnormalities occurring in conjunction with other craniofacial dysplasias seem far less prominent than could be anticipated based on their oftendisfiguring nature. Hemimandibular hyperplasia and elongation undoubtedly constitute the most obscure conditions that are associated with prominent, often unilateral, abnormalities of condylar, and mandibular growth. Finally, disturbances of mandibular growth as a result of juvenile idiopathic arthritis (JIA) and condylar fractures seem to be direct consequences of inflammatory and/or mechanical damage to the condylar cartilage.

Introduction

The size of the mandible, including the corpus, ramus, and condyle, as well as the timing and amount of condylar growth, vary considerably between individuals. Factors potentially contributing to this individual variation are the extent of masticatory action related to the consistency of the diet (Kiliaridis *et al.*, 1999) and, as shown recently (Van Erum *et al.*, 1997; Zhou *et al.*, 2005), genetic predisposition.

Distinct from even extreme cases of individual variation, the deviations from normality considered in this review constitute examples of abnormal mandibular and/or condylar growth that are related to truly pathological alterations. Based on their aetiology and time of appearance, they can be classified as (1) congenital malformations with associated growth disorders, (2) primary growth disorders, and (3) acquired diseases or trauma with associated growth disorders.

Congenital malformations with associated growth disorders

The most prevalent craniofacial malformation involving mostly unilateral condylar and ramal underdevelopment, as well as greatly variable abnormalities of the external and middle ear, is hemifacial microsomia [HFM; (Online Mendelian Inheritance in Man database of Johns Hopkins University: <http://www.ncbi.nlm.nih.gov/sites/entrez?db=omim>) OMIM 164210] with an estimated frequency of about 1/5000–6000 live births. Because of the similarity with the

manifestations of Goldenhar syndrome that is characterized additionally by vertebral defects and epibulbar dermoids, the two conditions have been combined under the term oculo-auriculo-vertebral (OAV) spectrum (Gorlin *et al.*, 2001). Its aetiology seems to be heterogeneous. Genetic factors, in particular chromosomal anomalies such as deletions of 5p, 6q, 8q, 18q, and 22q; duplications of 22q; and trisomies 7, 9, 18, and 22, have been implicated with the OAV spectrum. On the other hand, anomalies similar to those of HFM and Goldenhar syndrome resulted from early foetal exposure to thalidomide or retinoic acid (Gorlin *et al.*, 2001). In fact, a HFM-like phenotype could be reproduced using triazine, an anti-cancer drug, in mice and thalidomide in monkeys (Poswillo, 1973). Poswillo (1973) suggested that haemorrhages at the anastomosis of the external carotid and stapedial artery were responsible for the anomalies that seemed to increase in severity with the extension of local tissue damage. However, there is also considerable overlap in manifestations of the OAV spectrum, the retinoic acid syndrome, and the DiGeorge syndrome (OMIM 188400), a condition attributed to the loss of the T-box transcription factor TBX1 due to chromosomal deletion 22q11.2 (Botto *et al.*, 2003; Packham and Brook, 2003). Common to all of these three entities are cono-truncal cardiovascular defects, which led Johnston and Bronsky (1995) to suspect that defective neural crest cell development could be the primary cause of HFM.

The extent of temporomandibular joint (TMJ) involvement in the OAV spectrum largely determines the timing and type of treatment (Caccamese *et al.*, 2006). Therefore, HFM is often classified based on the degree of TMJ dysmorphology

(Mulliken and Kaban, 1987). The mildest forms (Kaban type I), such as the example shown in Figure 1a,b, appear to be characterized by a slightly hypoplastic mandibular condyle and thinner than normal condylar cartilage, but fairly normal hypertrophy of the chondrocytes and endochondral ossification (Figure 1c,d). Hence, mandibular growth can be expected to be only slightly deficient, justifying the recommendation to treat these cases at skeletal maturity using conventional orthognathic procedures (Caccamese *et al.*, 2006). In contrast, the severe forms of HFM (Kaban type III), such as the case illustrated in Figure 1e,f, exhibit aplasia or severe hypoplasia of the condyle. Even if present, these condyles seem to completely lack condylar cartilage and endochondral ossification (Figure 1g,h). Hence, mandibular growth on the affected side most likely comes to an early standstill; facial asymmetry must be assumed to worsen progressively, and early intervention utilizing, for example, rib grafts seems indicated to avoid secondary tilting of the maxilla.

Unlike the manifestations of the OAV spectrum, those of mandibulofacial dysostosis (MFD) are always bilateral. The prototype MFD, Treacher Collins syndrome (TCS; mainly in Europe also known as Franceschetti-Zwahlen-Klein syndrome; OMIM 154500), occurs at a frequency of about 1/25 000–50 000 live births. Abnormalities include underdeveloped supraorbital ridges, downward sloping of the palpebral fissures, and hypoplasia of the zygomatic bones, as well as of the mandibular rami and condyles (Gorlin *et al.*, 2001).

TCS is an autosomal dominant disorder with variable expressivity. Although MFD can also be caused by chromosomal abnormalities (Stevenson *et al.*, 2007), most individuals with TCS bear a mutation of the *TCOF1* gene. However, even among carriers of such a specific genetic defect, the phenotype varies markedly and is sometimes so mild that the disorder may go undetected clinically (Teber *et al.*, 2004). *TCOF1* encodes Treacle, a nucleolar protein. When it is defective, the biogenesis of

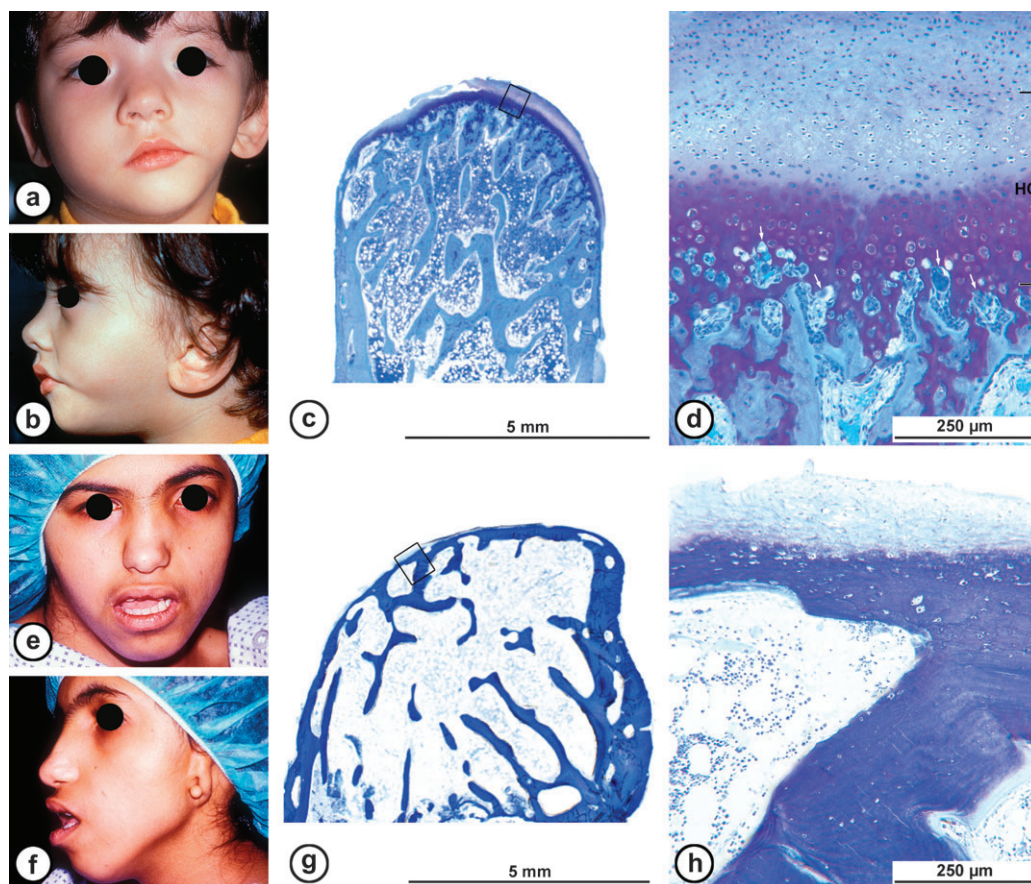


Figure 1 Hemifacial microsomia (HFM). (a–d) A 1.5-year-old girl with marked chin deviation (a), but mild involvement of the external ear (b) associated with HFM on the left side; (c) overview micrograph of the left condyle replaced by a costochondral graft and (d) detail of condylar cartilage marked by the rectangle in (c); note the diameter of the condyle (c) and the thickness of the hypertrophic cartilage (HC; d) that are approximately two-thirds of the dimensions seen in an age-matched healthy specimen; in contrast, endochondral ossification (d; arrows) is inconspicuous. (e–h) A 14-year-old girl with marked chin deviation (e) and severe involvement of the external ear (f) due to HFM on the left side. The overview micrograph of the resected condyle (g) and the detail of the condylar articular surface (h) marked by the rectangle in (g) reveal that the condyle is small for the age and condylar cartilage is completely missing. (c, d, g, and h) toluidine blue; original magnifications (c and g) $\times 6.3$ and (d and h) $\times 80$.

mature ribosomes in neuroepithelial and neural crest cells is impaired, the formation and proliferation of neural crest cells is disturbed and, finally, the number of neural crest cells that migrate into the branchial arches is deficient (Dixon *et al.*, 2006).

In agreement with this pathogenetic mechanism, the examination of a male foetus of 130 mm crown-rump length diagnosed as having TCS revealed that at this early pre-natal stage, the developing maxillary and zygomatic bones were hypoplastic. As far as the mandible was concerned, the rami and corpus were unusually short and abnormally shaped, while condylar cartilage was missing on one side and markedly deficient on the other side (Behrents *et al.*, 1977). On the other hand, clinical and cephalometric findings from TCS patients repeatedly show that the craniofacial skeletal pattern observed during infancy remained fairly stable during further development (Roberts *et al.*, 1975; Posnick and Ruiz, 2000). In fact, longitudinal changes in the length of the mandible reported by Roberts *et al.* (1975) appear to deviate little from control values, suggesting that the disorder of post-natal condylar growth associated with TCS may be far less extensive than the primary, pre-natal establishment of an abnormal skeletal pattern.

A clinically significant entity, also involving potential condylar growth problems, is the Pierre Robin sequence (PRS; OMIM 261800) with a prevalence of about 1/2000–8500 live births. It is characterized by mandibular micrognathia, cleft palate, and glossoptosis (Gorlin *et al.*, 2001). Although the aetiology of the disorder so far has not been elucidated, a recent systematic analysis of several PRS patients and the finding of a familial translocation of chromosomes 2 and 17 in one case suggested that genetic defects of *SOX9*, a gene encoding a transcription factor that is crucial for the differentiation of chondrocytes and chondrogenesis, could play a role in the development of PRS (Jakobsen *et al.*, 2007).

A first issue of ongoing debate with respect to PRS applies to the role played by tongue interposition as the cause for the formation of isolated palatal clefts. It has been argued that palatal clefts result from insufficient downward-forward displacement of the tongue due to a retroposition of the mandible. Alternatively, development of the tongue itself could be defective and result in insufficient displacement of the mandible. From the analysis of mice carrying a genetic defect predisposing to the development of a phenotype resembling PRS, Schubert *et al.* (2005) concluded that primary mandibular retrognathia, rather than deficient growth of the tongue, was responsible for the formation of the clefts. It should be borne in mind, however, that downward and forward growth of the mandibular arch prior to the fusion of the secondary palate is accounted for by Meckel's cartilage, rather than secondary condylar cartilage that develops considerably later (Diewert, 1982, 1985). When considering this, the suggested aetiological

involvement of defects in *SOX9* (Jakobsen *et al.*, 2007) appears quite conceivable.

A second controversial issue related to PRS is the question as to whether catch-up mandibular growth is able to compensate, at least in part, for the mandibular deficiency. While Figueroa *et al.* (1991) supported the possibility of catch-up growth, Laitinen and Ranta (1992), Hermann *et al.* (2004), and, recently, Eriksen *et al.* (2006) showed that post-natal growth of the mandible in children with PRS is normal and comparable with that of other children with clefts. Also, children with PRS associated with mandibular hypodontia had smaller mandibles than subjects with PRS and all permanent mandibular teeth, and this pattern did not improve with further growth (Suri *et al.*, 2006).

In addition to these relatively frequent syndromes, there are additional, but very rare conditions affecting the size and shape of the mandible and possibly also condylar growth. Examples are acrofacial dysostosis 1 (OMIM 154400) or Nager syndrome, that can be associated with condylar ankylosis (Halonen *et al.*, 2006), and Turner syndrome with a short mandibular body and posterior rotation of the mandible (Peltomäki *et al.*, 1989; Rongen-Westerlaken *et al.*, 1993; Babić *et al.*, 1997; Perkiömäki *et al.*, 2005). Hemifacial atrophy (OMIM 141300) or Parry-Romberg syndrome may affect mandibular growth and lead to progressive facial asymmetry (Buonaccorsi *et al.*, 2005), while Hallerman-Streiff syndrome (OMIM 234100) is characterized by a narrow upper dental arch, extensive hypodontia, and a very small, posteriorly rotated mandible, giving the impression of a 'bird face' (Defraia *et al.*, 2005).

In Silver-Russell syndrome (OMIM 180860), the mandible as well as the maxilla are small and retrognathic. Left-right differences in mandibular growth causing facial asymmetries are common (Kotilainen *et al.*, 1995). Similarly, children with Marfan syndrome (OMIM 154700), a connective tissue disorder resulting from mutations in the *FBN1* gene that encodes the microfibril component fibrillin-1, often have a retrognathic maxilla and mandible (Westling *et al.*, 1998).

Although less common than mandibular hypoplasia, oversized mandibles do occur in association with some syndromes. Acromegaly is a condition of growth hormone overproduction. When the disease becomes manifest, the mandible enlarges rapidly and a progenic habit develops, sometimes in combination with sleep apnoea syndrome due to changes in the laryngeal soft tissues. Recently, an inherited form of acromegaly due to a germ-line mutation in the *AIP* gene (OMIM 605555) has been detected. As a result, the defective aryl hydrocarbon receptor-interacting protein leads to a predisposition for pituitary adenoma (Georgitsi *et al.*, 2007). In Proteus syndrome (OMIM 176920) that is characterized by striking facial abnormalities, one of two subforms shows unilateral condylar overgrowth causing progressive craniofacial asymmetry (Kreiborg *et al.*, 1991). The stimulating influence of sex chromosomes

on the growth of the mandible can be clearly seen in patients with Klinefelter's syndrome (47,XXY). In comparison with normal control females, these individuals have larger mandibles, in particular larger mandibular bodies, which cause marked mandibular prognathism.

Finally, there are craniofacial malformations that do not affect the jaws directly, but lead to indirect, presumably compensatory, alterations of otherwise relatively normal condylar growth. For example, in cases of craniosynostoses such as Crouzon (OMIM 123500), Pfeiffer (OMIM 101600), and Apert (OMIM 101200) syndromes, unusual transverse mandibular growth may be regarded as an attempt at adapting to the impaired expansion of the cranial vault (Boutros *et al.*, 2007).

In summary, disorders of mandibular and condylar growth associated with craniofacial malformations appear far less extensive than could be expected, when considering the mostly markedly disfiguring conditions. Rather than disturbed growth, the primary establishment of an aberrant craniofacial skeletal pattern seems to account for the clinical impression of abnormality. Obvious exceptions from this rule are, however, severe cases of HFM, where unilaterally deficient or completely absent condylar growth results in progressive facial asymmetry.

Primary growth disorders

Condylar hyperactivity can be clearly identified only when it occurs unilaterally. Bilateral symmetric cases are very difficult to delineate against mandibular prognathism and seem to be very rare (Obwegeser, 2001). Unilateral condylar hyperactivity typically becomes apparent at some time during the growth period, most often during childhood. Hence, it constitutes a true disorder of growth (Obwegeser, 2001). The aetiology is largely unknown. There are reports of cases where condylar trauma during childhood later manifested itself as hyperplastic growth (Jacobsen and Lund, 1972; Rubenstein and Campbell, 1985). Other possible causes taken into consideration, but so far not substantiated, are inflammation, hypervascularization, and unspecified genetic factors (Obwegeser, 2001).

In the literature, condylar hyperactivity is commonly referred to as condylar hyperplasia. This term was coined by Rushton (1944, 1946), although it did not go unnoticed that apart from the condyle, the entire ramus and corpus of the hemimandible on the affected side were enlarged, resulting in gross distortion of the lower face without significant deviation of the chin (Figure 2a). However, unilateral condylar hyperactivity can also manifest itself in elongation, rather than increase in volume, of the condylar neck, ramus, and corpus, leading to facial asymmetry with marked deviation of the chin to the unaffected side (Figure 2b). For this form of growth anomaly, Obwegeser and Makek (1986) introduced the term hemimandibular elongation

and referred to the disorder described by Rushton (1944, 1946) as 'hemimandibular hyperplasia'.

Considering that the entire hemimandible, rather than only the mandibular head, is affected in cases of unilateral condylar hyperactivity irrespective of the clinical classification, the question arises whether the causative disturbance really lies in the condyle. Most previous reports on histological findings, reviewed recently by Luder (2001), mentioned alterations of the condylar cartilage that seemed to indicate unusually rapid growth and/or an abnormally long duration of growth. Slootweg and Müller (1986) even suggested a classification of condylar hyperplasia based on the appearance of the cartilage. However, compared with normal age-matched specimens, differences in cartilage morphology and thickness proved rather small (Luder, 2001). Thus, given the variation in the timing of mandibular growth (Björk, 1963), caution seems to be warranted when drawing conclusions as to individual growth velocity based on the appearance of the condylar cartilage.

Another structural feature observed consistently in hyperplastic condyles is the distribution of cartilage rests in the subchondral spongiosa. As noted by Rushton (1944), remnants of cartilage matrix occur at abnormally large distances from the front of the erosion. When comparing the various forms of condylar hyperactivity, this seems to be particularly true for cases of hemimandibular hyperplasia that additionally reveal a conspicuous arrangement of mixed cartilaginous-bony trabeculae lacking a clear orientation (Figure 2c). In contrast, condyles from subjects with hemimandibular elongation exhibited cartilage of normal structure and thickness, subchondral cartilage rests at normal distances from the zone of erosion, and a spongiosa comprising well-orientated bone trabeculae (Figure 2d; Luder, 2001).

These findings indicate that in cases of condylar hyperactivity, the primary vascular invasion and resorption of cartilage, that determine its thickness, are fairly normal or at least keep pace with cartilage growth. In contrast, remodelling of the primary spongiosa, that is responsible for the ultimate removal of cartilage remnants and arrangement of the bone trabeculae, may be disturbed or unbalanced in hemimandibular hyperplasia, but normal in hemimandibular elongation (Luder, 2001). It is, thus, possible that distinct pathogenetic mechanisms account for the two clinical forms of condylar hyperactivity, although this has yet to be confirmed by additional, more comprehensive studies.

The question as to whether condylar growth is active or has ceased is critical for selecting the appropriate treatment procedure. When growth is still ongoing, high condylectomy, although controversial, is considered an option to avoid secondary, adaptive deformation of the maxilla. On the other hand, corrective orthopaedic surgery should be envisaged only when condylar growth has ceased (Marchetti *et al.*, 2000; Obwegeser, 2001; Deleurant *et al.*, 2008). As

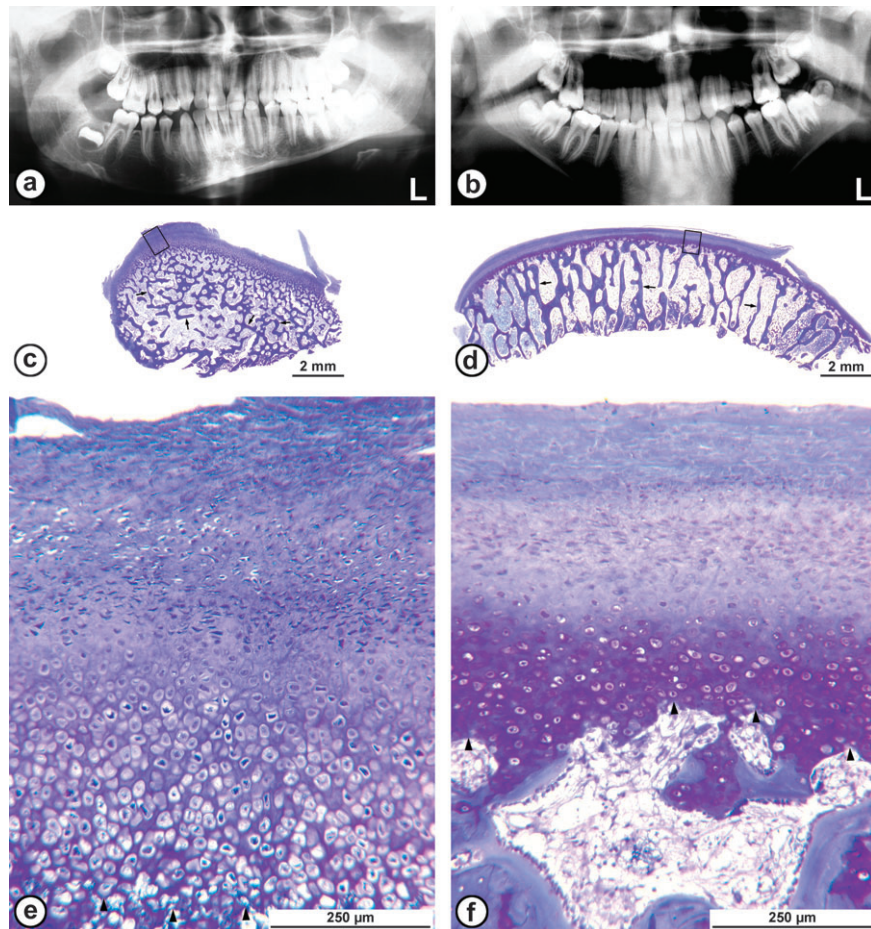


Figure 2 Hemimandibular hyperplasia (HH; a, c, and e) and hemimandibular elongation (HE; b, d, and f). Dental pantomographs of a 12-year-old boy (a) and a 13-year-old girl (b); note the distortion of the entire right hemimandible associated with HH (a) and the midline deviation to the left due to HE on the right side (b). (c–f) Overview micrographs of the condyles (c and d) resected in the subjects shown in (a) and (b) and details of the condylar cartilage (e and f) marked by the rectangles in (c) and (d), respectively; note the arrangement of the subchondral bone trabeculae (c and d; arrows) and the front of endochondral ossification (e and f; arrowheads). (c–f) toluidine blue; original magnifications (c and d) $\times 6.3$ and (e and f) $\times 80$.

the method of choice for the assessment of condylar growth activity, planar or three-dimensional quantification of 99m technetium methylene diphosphonate (99m Tc-MDP) uptake using plane scintigraphy or single photon emission computed tomography are strongly recommended (Chan *et al.*, 2000; Pripatnanont *et al.*, 2005). However, it should be borne in mind that all these methods of bone scanning, although highly sensitive, are non-specific, that is they do not yield any clue as to the reason for an observed asymmetry in condylar activity (Obwegeser, 2001).

Acquired diseases or trauma with associated growth disorders

Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disease of unknown aetiology, which is present for longer than 6 weeks and starts before the age of 16 years (Petty *et al.*, 1998). It comprises seven subtypes (systemic arthritis, rheumatoid factor-negative and -positive polyarthritis,

oligoarthritis, enthesitis-related arthritis, psoriatic arthritis, and others) based on clinical symptoms during the first 6 months of the disease. Overall, JIA is the most common form of arthritis in children. Its frequency is about 1–2/1000 in most populations (Saurenmann *et al.*, 2007) with a ratio of girls to boys of about 3:2 (Andersson Gäre *et al.*, 1987). The disease is characterized by variable degrees of joint inflammation, joint destruction, and progressive disability (Palmisani *et al.*, 2006).

Although the aetiology of JIA is unknown, it has clear autoimmune characteristics. There is, however, no evidence indicating that some specific antigen is responsible. Rather, it is presumed that many different factors, to varying degrees, lead to the outbreak of the disease (Sen, 2005). For this reason, the serological demonstration of HLA-B27, antinuclear antibodies, and rheumatoid factor are of little prognostic value for the course of JIA (Ilwite, 2002).

Histopathologically, JIA is characterized by hypertrophic inflammatory synovitis with cellular infiltration and

proliferation of blood vessels. In the chronic state of the disease, the articular surfaces are covered by a pannus, a tumour-like mass of inflamed granulation tissue. The expansion of the pannus is enhanced by extensive formation of new blood vessels and results in cartilage and joint destruction that may occur early in the course of the disease (Yang *et al.*, 2002).

Reported frequencies of TMJ involvement in JIA vary from approximately 17 to 87 per cent, probably depending on whether all subtypes of the disease have been taken into account and whether the diagnoses have been based on a purely clinical, a radiological, or even a magnetic resonance imaging (MRI) examination (Mayne and Hatch, 1969; Rönning *et al.*, 1974; Kùseler *et al.*, 1998; Billiau *et al.*, 2007). In all subtypes, one or both TMJs can be affected and may even be the initial joints involved (Karhulahti *et al.*, 1990; Kùseler *et al.*, 1998; Martini *et al.*, 2001). While Billiau *et al.* (2007) claimed that condylar damage was unrelated to JIA subtype and disease activity, severity, or duration, Säilä *et al.* (2004) reported that patients reacting positive for antinuclear antibodies more frequently exhibited TMJ involvement than histocompatibility locus antigen-positive individuals, and Pedersen *et al.* (2001), based on a study using enhanced MRI, concluded that TMJ involvement was particularly frequent in polyarticular onset JIA. Also based on MRI, Kùseler *et al.* (2005) found a prevalence of 26 per cent for pannus formation in the TMJ and a frequency of 71 per cent regarding condylar erosions.

Because of its suitability to detect even small initial destructive lesions, MRI has become the gold standard for TMJ examinations in subjects with JIA (Figure 3). It has even been suggested that a panoramic examination is not indicated when a MRI is obtained (Arabshahi and Cron, 2006; Helenius *et al.*, 2006). High-resolution ultrasonography (US) has been proposed as an alternative to MRI, because it can be used while the joint is functioning, thus allowing

assessment of disc movements (Jank *et al.*, 2007). However, a closer look at the publication of those authors shows that only severe destructive TMJ changes had been investigated. In agreement with this observation, a recent, unpublished pilot study indicated that US is not able to detect early TMJ arthritis before destructive alterations have occurred. These results suggest that while US is a valuable diagnostic imaging method for the TMJ, it cannot yet replace a MRI investigation.

Histopathologically, JIA seems to affect the lower and upper TMJ compartments to markedly different degrees. In TMJs exhibiting severe radiographic alterations where condylar replacement with costochondral grafts seemed indicated, the entire lower joint compartments were filled with masses of granulomatous tissue, while the upper compartments appeared macroscopically healthy. In contrast, condyles showed localized to total cartilage destruction and prominent inflammatory infiltrates of the subchondral bone marrow (Svensson *et al.*, 2001). Evidence regarding the pathogenesis of cartilage destruction is available only from investigations of rheumatoid arthritis and osteoarthritis, both of which occur in adulthood and, therefore, do not result in growth disturbances, although they may entail marked remodelling of articular tissues. According to these studies (Kanyama *et al.*, 2000; Miyamoto *et al.*, 2002; Gepstein *et al.*, 2003; Goldring, 2003; Tiilikainen *et al.*, 2005; Mälemud, 2007), inflammatory cells populating the synovial membrane release pro-inflammatory cytokines, chemokines, angiogenic factors, and proteinases. Among the secreted products that appear to exert the greatest effect on cartilage loss are interleukin-1 (IL-1) and tumour necrosis factor α (TNF α). The most potent angiogenic factor is vascular endothelial growth factor which plays a critical role, because it enhances growth of the vasculature in the inflamed synovial tissue. IL-1 stimulates chondrocytes to produce matrix metalloproteinases (MMPs) which, in their active

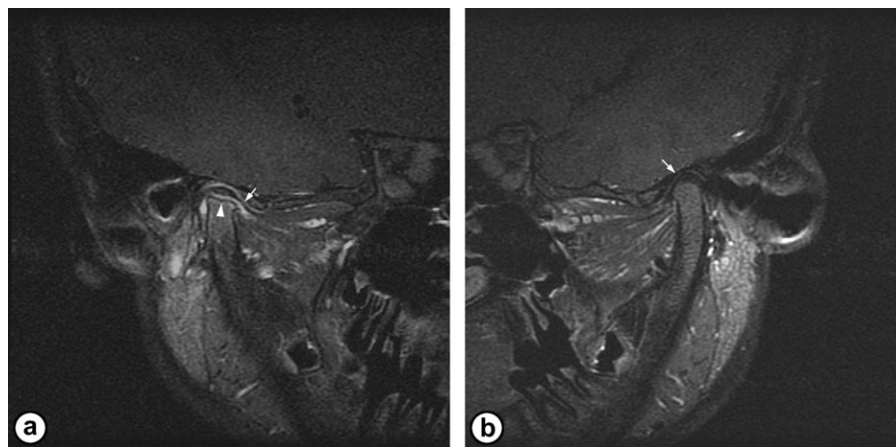


Figure 3 Juvenile idiopathic arthritis (JIA). Lateral magnetic resonance views of the right temporomandibular joint affected by JIA (a) and the contralateral healthy joint (b) of a 13-year-old girl; note the erosion of the right condyle (a; arrowhead) and the position of the intermediate zone of the articular discs (a and b; arrows).

forms, effectively degrade collagens and proteoglycans. In addition, members of the aggrecanase (ADAMTS) family, particularly ADAMTS-4 and ADAMTS-5, seem to participate in cartilage destruction (Yoshida *et al.*, 2006). Interestingly, both MMPs and aggrecanases are also involved in remodelling processes elicited by experimental changes in dietary loading (Pirttiniemi *et al.*, 2004; Yu *et al.*, 2007).

JIA involving the TMJ is associated with characteristic facial changes, in particular a short mandibular ramus and backward-rotated mandibular corpus, prominent antegonial notching, and mandibular retrognathia (Rönning *et al.*, 1974; Björk and Skieller, 1985; Hanna *et al.*, 1996; Mericle *et al.*, 1996; Kjellberg, 1998). Whereas Twilt *et al.* (2006) found that in comparison with age-matched healthy individuals, patients with JIA, regardless of their TMJ status, exhibited retrognathia and posterior rotation of the mandible, craniofacial alterations were reported by Billiau *et al.* (2007) to be related to the presence of radiographic condylar damage, even if this may be mild. Notably, however, bony erosion seems to occur later in JIA than in adult rheumatoid arthritis (Barriga *et al.*, 1974), and condylar resorption seems to be present for some time before bone destruction is radiographically detectable (Küseler *et al.*, 1998; Twilt *et al.*, 2006). Thus, the destruction of condylar cartilage, irrespective of its severity, appears to entail significant disturbances of mandibular growth. On the other hand, recent longitudinal studies (Twilt *et al.*, 2007, 2008) revealed that radiographic signs of condylar damage completely disappeared in about half and improved in another fifth of examined patients, while they worsened in a few subjects that exhibited particularly high disease activity.

Abnormal position or displacement of the TMJ disc has emerged relatively recently as a possible cause of mandibular growth disturbances. Disc disorders are anything but rare in childhood. While no cases of abnormal disc position could be detected in a sample of children ranging in age from 2 months to 5 years (Paesani *et al.*, 1999), Ribeiro *et al.* (1997) observed dislocated discs in 11 per cent of children aged from 6 to 11 years. Also, audible joint sounds, which may be associated with disc disorders, are relatively frequent, even in clinically healthy children. Heikinheimo *et al.* (1989) reported a frequency of 25–27 per cent, while Henrikson *et al.* (2000), as well as Henrikson and Nilner (2000), noticed joint sounds, although with fluctuating intensity, in 39 per cent of the children examined.

In an experiment using growing rabbits, the surgical induction of unilateral anterior disc displacement resulted in an asymmetric reduction of ramal growth and mandibular length, before visible osteoarthrotic TMJ changes developed (Legrell and Isberg, 1998, 1999; Legrell *et al.*, 1999). The authors suggested that disc dislocation *per se* had a primary adverse effect on condylar growth. Supporting these findings, Bryndahl *et al.* (2006) showed that

bilateral anterior disc displacement in a growing animal causes significant mandibular retrognathia. As complete maxillomandibular immobilization does not seem to affect mandibular growth in spite of significant histological alterations in condylar cartilage (Isacsson *et al.*, 1993), it is doubtful that the observed disturbances of condylar growth resulted from a mechanical impairment of anterior condylar excursions, which conceivably could have been caused by the displaced disc. Alternatively, the adverse effects on condylar growth could also have been the consequence of an altered masticatory function (Legrell and Isberg, 1998, 1999). On the other hand, an experimental disc perforation created in growing rabbits initially led to increased cell proliferation in the condylar cartilage. At longer intervals following surgery, distinct arthrotic changes, comprising osteophytes and flattening of the condyle developed, but at still later time points, these changes were milder, suggesting some local adaptation to the disc perforation (Narinobou *et al.*, 2000).

Mandibular trauma during childhood involves the condylar region in 36–50 per cent of subjects (Baumann *et al.*, 2004). Mandibular fractures are estimated to be about twice as frequent as noticed or diagnosed, as many of them occur during early childhood and often pass with little discomfort. The consequences of a trauma to the condyle depend on its location. In the case of intracapsular fractures, the fragments are seldom severely dislocated, but there is an increased risk for ankylosis, particularly in children younger than 3 years of age (Baumann *et al.*, 2004). If the fracture affects the condylar neck and, thus, is extracapsular, the condylar head often becomes dislocated, almost always in a forward-medial direction.

Long-term complications of both intra- and extracapsular fractures, such as the development of facial asymmetry or mandibular retrognathism and anterior open bite as well as TMJ ankylosis or painful temporomandibular disorders, seem to be rare and, if present, mild (Kellenberger *et al.*, 1996; Marianowski *et al.*, 2003). A new condyle can even be generated and facial symmetry may thus be recovered. An ankylosis of the TMJ as a consequence of a childhood condylar trauma is very rare (Marianowski *et al.*, 2003). In a prospective study of 38 growing patients with fractures of the condylar neck, Lund (1974) found that in a majority of the subjects, greater than normal, compensatory growth occurred on the affected side, and no significant facial asymmetry developed. In the same study, a remarkable potential for post-traumatic condylar remodelling was noticed, which in some instances resulted in close to complete regeneration of a new mandibular head.

This potential for remodelling is demonstrated in the case of a 22-year-old female illustrated in Figure 4. As a consequence of a bicycle accident, she suffered a fracture of the left mandibular neck with forward-medial displacement of the condyle (Figure 4a,b). Conservative functional treatment was started only 1 week later, when she finally

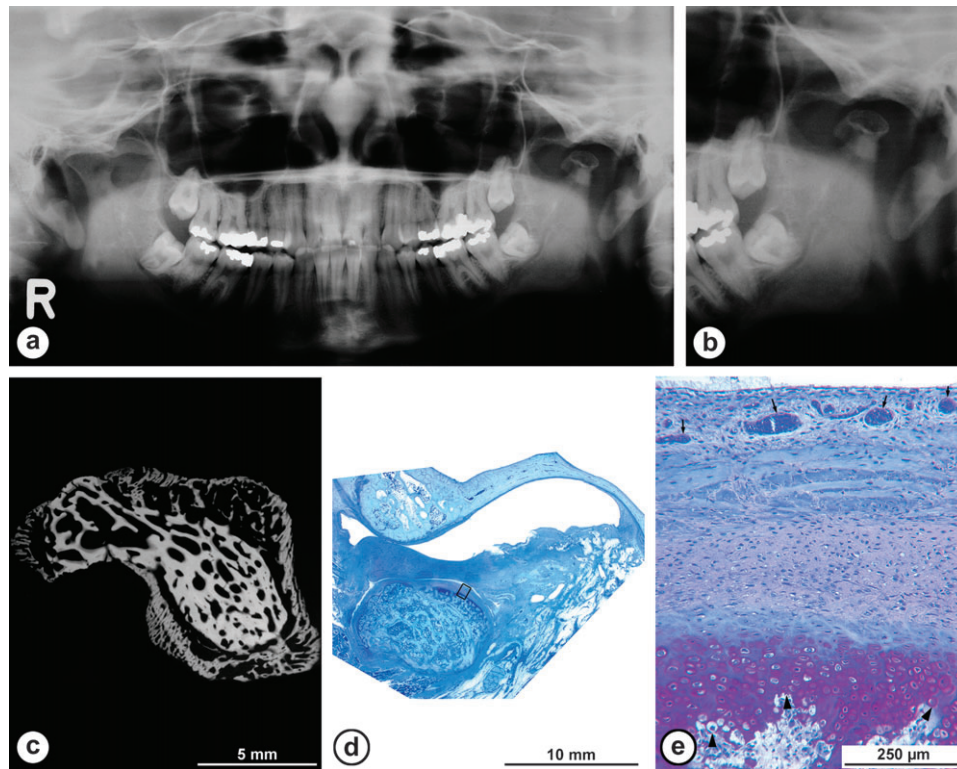


Figure 4 Condylar fracture. Dental pantomographs (a and b) of a fracture of the left condyle suffered by a 22-year-old female as a consequence of a bicycle accident. Microradiograph of the left condyle (c), overview micrograph of the left temporomandibular joint (d), and detail of condylar cartilage (e) marked by the rectangle in (d) 2.5 months after the accident; note the old (light) and newly formed (dark) condylar bone (c), the dislocation of the condyle relative to the mandibular fossa (d) as well as in (e) the unusual vascularization of the articular fibrous layer (arrows) and presence of hypertrophic cartilage and endochondral ossification (arrowheads). (d and e) Toluidine blue; original magnifications (c) $\times 6.3$, (d) $\times 3$, and (e) $\times 80$.

went to see an emergency doctor. Two and a half months after the accident, she died from a cause unrelated to the first event, and an autopsy was carried out. The dislocated condyle exhibited conspicuous vascularized connective tissue underneath the articular surface and hypertrophic cartilage involved in endochondral ossification (Figure 4d,e), which could not be expected in a normal mandibular head of a female of this age. As a result of endochondral ossification, a remarkable amount of new bone had apparently been formed at the insertion of the lateral pterygoid muscle as well as at the zenith and posterior slope of the condyle (Figure 4c). The location of the hypertrophic cartilage and new bone formation gave the impression that reactivated condylar growth tended to re-establish a normal condyle–fossa relationship. Although no final conclusion can be drawn, this conceivably could have occurred in response to tension exerted by the stretched capsular apparatus, to post-traumatic inflammatory processes, or to a combination of both.

Owing to the significant progress in research techniques, our knowledge regarding the aetiology and pathogenesis of disorders affecting condylar cartilage has increased considerably during the last decades. At the same time, the diagnostic possibilities of the TMJ have improved greatly and allow early diagnoses of initial pathological processes.

It is to be hoped that continuing efforts in basic and clinical research will eventually shed light on the remaining obscure forms of mandibular growth disorders and allow the design of new strategies for their prevention and treatment.

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